REMARKS

Claims 1, 5-12 and 23-26 have been withdrawn. Claims 2-4, 13-22 and 27-31 are now pending. The amendment of the claims has necessitated a change in inventorship. The inventors of the present claims are William E. Jack and Andrew Gardner. A request for deletion of inventors Philip Buzby and James DiMeo is attached to this response.

The Examiner is thanked for the courtesy of a telephone interview on May 2, 2006. As a result of the interview, Applicants have amended the claims to place them in a condition of allowance. The amendment includes limiting independent claims 2 and 3 to the use of acyclonucleotides and incorporating the subject matter of claim 12 into claim 2 and the subject matter of claim 9 into claim 3 to further define the family B polymerases. This step of simplifying the claims is to facilitate allowance of the claims although it is believed that the full scope of the claimed invention before amendment is properly enabled and described. Claimed subject matter relating to derivatized dideoxynucleotides and derivatized acyclonucleotides has been withdrawn without prejudice for prosecution in a subsequent filed continuation application.

Description and Enablement rejection under 35 USC 112 first paragraph

The Examiner has rejected claims 1-7, 11, 14-17 and 19-31 under 35 USC 112 first paragraph and also 1-12, 14-17 and 19-31 under 35 USC 112 first paragraph for what seems to be the same reasons. In both cases, the Examiner asserts that the Applicants are not in possession of the claimed invention and have not enabled the invention on the basis that Archaeon B-polymerases could be a diverse group of polymerases with unexpected and

differing substrate specificities. In making this rejection, the Examiner has stated that the significant discussion of the remarkable sequence homogeneity of this group of polymerases in the description of the invention that was further listed in the response to the first action has failed to convince him. The Examiner further reiterated this position in the telephone interview of May 2, 2006.

DNA polymerases are enzymes that occur in nature for the purpose of polymerizing nucleotide triphosphates in an order that is complementary to a nucleotide sequence on a DNA template. Family B polymerases are a subgroup of DNA polymerases. The subgroup of Family B polymerases has been further limited for the purposes of the present claims to archaeon Family B polymerases. Archaeon B polymerases have been claimed in Patent US 5,500,363 according to sequence homology under specified hybridization conditions. Because this definition was found acceptable to the USPTO as fulfilling description and enablement requirements for this class of enzymes, this definition is inserted into claim 2. The limitation of amino acid sequence identity incorporated into claim 3 also defines the Family B polymerases for use in the method very specifically.

In the present claimed method as amended, the archaeon type B polymerase is reacted with an acyclonucleotide, which becomes incorporated into the newly synthesized DNA at the 3' terminal.
The Examiner asserts that the specification lacks sufficient description concerning:
(1) common structure of Family B polymerases
(2) structure-function relationship
(3) how to isolate an archaeon Family B DNA polymerase and
(4) how to test it to determine efficacy.

Common structure of Family B polymerases

Applicants have provided a detailed analysis of support provided in the description of the invention relating to the homogeneity of this group of enzymes (see Response dated 4/14/05).

Structure-Function Relationships

It is well known in protein chemistry that an enzyme has an active site that has a structure that is suited for binding a substrate in such a way to lower the energy of the reaction so as to catalyze a reaction. The structure of the active site determines its function. Random mutations of amino acids within the active site can disrupt the catalytic function of the enzyme. When a particular type of enzyme obtained from a variety of sources proves to have a conserved sequence that results in a homogeneous active site, it is reasonable to assume that this type of enzyme from the different sources act in the same way. If this is demonstrated conclusively for 4 enzymes of the same type from diverse sources, it is reasonable to assume that this property is consistent with this type of enzyme. If a modified substrate is found to bind effectively to the active site of one of these enzymes this is highly suggestive that the modified substrate will bind in a similar way with all members of this class of enzyme. If this observation is shown conclusively for 4 enzymes of a single type from 4 diverse sources, this finding is generally considered conclusive.

The request by the Examiner for more information about the molecular mechanism of action between the substrate and the active site would not make this case more persuasive than it already is. The archaeon family B

polymerase is defined in the amended claims by a stringent DNA hybridization to defined DNA sequence encoding the enzyme such that its interaction with the claimed substrate is defined without ambiguity. To further emphasize the points made in this section, applicants submit a declaration under oath (the Jack declaration) of the strong degree of predictability of the structure-function relationship of this group of polymerases and an acyclonucleotide substrate.

How to isolate an archaeon Family B DNA polymerase

Applicants respectfully direct Examiner to the description in the specification, which addresses both these issues in comprehensive detail. Page 10 has a section entitled " IDENTIFYING DNA POLYMERASES WITH SIMILAR PROPERTIES". DNA and amino acid sequence searches using publicly available databases are described in silico with a specified search parameters, hybridization under specified conditions in vitro, and use of diagnostic antibodies specified in the prior art. Furthermore, the applicants describe not just 4 archaeon type B polymerases as asserted by the Examiner in page 5 of the office action dated 11/4/05. Table 3 lists 26 Family B polymerases with sequence homology of which 15 polymerases have an almost identical motif B of 15 amino acids corresponding to the active site of the polymerase.

It is well within the ability of a person of ordinary skill in the art to clone a polymerase if the sequence or even partial sequence of the enzyme is known. It is also well within the ability of a person of ordinary skill in the art to utilize a conserved sequence motif from a group of enzymes to identify from a database, a set of related sequences, each of which may be cloned.

How to test the DNA polymerase for efficacy

Example 1 on page 27 of the application is entitled: A TITRATION ASSAY TO MEASURE THE RELATIVE EFFICIENCY OF MODIFIED NUCLEOTIDE INCORPORATION. This example explains in detail how to determine the relative efficacy of modified nucleotide incorporation be the modified nucleotide be an acyclonucleotide or indeed any other modified nucleotide.

Applicants assert that the description of this assay in combination with a precise definition of the genus of Family B polymerases encompassed by the claims provide a full clear and exact description of the invention and a enabling description of how to reproduce the claimed invention. There is no basis to the Examiner's assertion that the desired biological characteristics are unpredictable and that undue experimentation would be required to practice the full scope of the invention. Consequently, applicants request that the Examiner reverse the rejection.

CONCLUSION

Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants petition for a three-month extension of time for responding to the Final Office Action and enclose check in the amount of $760.00 covering the extension fee and the fee for the enclosed notice of appeal. Please charge Deposit Account No. 14-0740 for any deficiencies.

Respectfully submitted,
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